Docket no.: 00776/0203006-US0
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Lisolette Bjerre Knudsen et al.

Application No.: 09/800,541 Confirmation No.: 4130

Filed: March 7, 2001 Art Unit: 1647

For: **LOWERING SERUM LIPIDS** Examiner: D. Romeo

REPLY BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Reply Brief, responsive to the Examiner's Answer dated April 5, 2005, is submitted in triplicate under 37 C.F.R. §1.193(b). A Request for Oral Hearing is submitted concurrently herewith.

I. Introduction

The Examiner has made several errors in his Answer. First, the Examiner's summary of the Status of Claims is incorrect. The full scope of the subject matter of the pending claims is pending and under consideration. Accordingly, the Examiner is mistaken to the extent that he asserts that anything less than the full scope of the pending claims is under consideration.

Second, the Examiner's rejection of the claims as anticipated by the prior art of record relies on an incorrect claim interpretation. The Examiner submits that the claim limitation "a patient in need of" includes all diabetics. Contrary to the Examiner's interpretation, however, "a

patient in need of" is properly construed as requiring an intent to achieve the result recited in the respective claims.

Third, the Examiner has improperly based anticipation on a combination of references. The Examiner adds Howard, 1994, *Curr. Opin. in Lipidology,* 5:216-220, to Eng and, separately, to Efendic, U.S. Patent No. 5,631,225, as disclosing that Eng or Efendic "would administer" exendin-3 or exendin-4 to diabetics with the intent to improve glycemic control and to improve diabetic dyslipidemia. The Examiner did not use Howard to explain Eng or Efendic. Rather, he used Howard to modify Eng and Efendic. It is improper to use a second reference to modify an alleged anticipatory reference.

Fourth, the Examiner wrongly shifted the burden of proving that the claims are enabled to Appellants without providing a reasonable basis to doubt the objective truth of the disclosure of the present specification.

Fifth, the Examiner has used the wrong legal standard for determining whether the specification provides sufficient written description for GLP-1 agonist analogues and derivatives. The numerous examples of GLP-1 agonist analogues and derivatives disclosed in the specification are sufficient written description for the GLP-1 agonist analogues and derivatives of the present claims.

Sixth, the Examiner can not support his assertion that Appellants' definitions of "analogue" and "derivative" are indefinite.

II. The Claim Summary in the Brief on Appeal Is Correct

Appellant's Brief on Appeal states correctly that claims 26-29 and 36-72 are pending, rejected, and appealed. These claims are currently directed to methods for (1) lowering

the levels of one or more serum lipids (*see* claim 26), (2) reducing the serum LDL:HDL ratio (*see* claim 37), or (3) reducing the serum level of lipoprotein A(lp(A)) and/or apolipoprotein A (apo(A))) (*see* claim 40), by administering an effective amount of a GLP-1 agonist selected from the group consisting of GLP-1 (7-37), GLP-1 (7-36)amide, exendin-3, exendin-4, or an analogue or derivative of any of the foregoing. No subject matter had previously been withdrawn by the Examiner and it is improper to withdraw any subject matter now. Accordingly, the full extent of the pending claims is under consideration.

The Examiner asserts that claims 26-29 and 36-72 are withdrawn from consideration to the extent that they are not directed to the elected species Arg^{34}, Lys^{26}(N-ε(-γ-Glu(Nα-hexadecanoyl)))GLP-1(7-37), and GLP-1 (7-36)amide, exendin-3, and exendin-4. Appellants had elected the claims of Group I, directed to therapeutic methods of administering a GLP-1 agonist. As part of the restriction requirement, the Examiner required election of a species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. No subject matter was withdrawn. The full scope of the claims should be considered here.

III. All of the Pending Claims Require Administering a GLP-1 Agonist With the *Intent* to Lower Levels of One or More Serum Lipid, Reduce the Serum LDL:HDL Ratio, or Reduce the Serum Level of Lipoprotein A (lp(A)) and/or Apolipoprotein A (apo(A))

The Examiner's rejection of the claims as anticipated by Eng or Efendic and for obviousness-type double patenting over U.S. Patent No. 6,268,343, claims 39 and 40 or, U.S. Patent No. 6,458,294, claims 19 and 20, is based on the mistaken conclusion that the respective references disclose or suggest administering certain GLP-1 agonists to a patient with the intent of lowering

levels of one or more serum lipid, reducing the serum LDL:HDL ratio, or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)). The Examiner has mistakenly read the intent to use a GLP-1 agonist for the claimed methods into the prior art.

A. The Examiner mistakenly reads intent into the prior art

The Examiner's Answer repeatedly cites Howard to "explain" Eng, Efendic, or the cited claims of U.S. Patents No. 6,268,343 and 6,458,924. What the Examiner is actually doing, however, is combining Howard to provide an intent that is absent from the prior art. Neither the primary references cited by the Examiner nor Howard provides the requisite intent to use a GLP-1 agonist for the presently claimed treatments. Moreover, Eng and Efendic cannot be combined with a secondary reference to anticipate. The Examiner asserts that Howard shows that a diabetic patient is a "patient in need" of the presently claimed treatments because (Examiner's Answer at page 6, lines 7-13 and repeated at page 8, last line through page 9, line 6; *See also* Examiner's Answer at page 23, lines 20-22 and page 24, lines 19-21):

> the treatment of diabetes overlaps the treatment of dyslipidemia, cardiovascular disease, hypertension, and obesity and that [the prior art references cited by the Examiner] would administer [the respective GLP-1 agonists disclosed therein] to a diabetic with the intention of improving glycemic control and improving diabetic dyslipidemia because the cornerstone of therapy for diabetic patients should essentially consider the management of dyslipidemia along with the hyperglycemia, hypertension, and obesity and agents which improve glycemic control sometimes also result in improvements in diabetic dyslipidemia"

The Examiner cannot use Howard's general desire to treat undesirable diseases that are sometimes (but not always) associated with diabetes to impart intent to practice the presently

claimed methods with a GLP-1 agonist because prior to the present application it was unknown that a GLP-1 agonist could be used to achieve the results in the presently claimed methods.

If one accepts the Examiner's logic, then treatment of diabetes alone would preempt claims to treating any condition that may ever be associated with diabetes. For example, one could say that treatment of diabetes overlaps a claim to treatment of diabetic retinopathy, as some diabetics exhibit diabetic retinopathy. Using the Examiner's logic would mean that Eng and Efendic should be construed as anticipating the administration of exendin/GLP to a diabetic patient with an intent to treat diabetic retinopathy. This is not the law.

As set forth in Appellant's Brief on Appeal, in *Jansen v. Rexall Sundown, Inc.*, the Federal Circuit held that the claim term "to a human in need thereof" used with reference to a method of treatment with a disclosed outcome recited in a claim "is a statement of the intentional purpose for which the method must be performed." *Jansen v. Rexall Sundown, Inc.*, 342, F.3d 1329, 68 U.S.P.Q.2d 1154 (Fed. Cir. 2003). Nothing in Howard can transform the prior art's intentional use of a GLP-1 agonist to treat diabetes or obesity into the intentional use of a GLP-1 agonist for the claimed methods of lowering levels of one or more serum lipid, reducing the serum LDL:HDL ratio, or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)). Intent is in the mind of the individual administering the GLP-1 agonist and, therefore, cannot be "imparted" by Howard.

B. The Examiner improperly uses the specification to bootstrap intent into the methods disclosed in the prior art

The Examiner asserts incorrectly that certain passages in the present specification define all diabetics as "a patient in need of" the presently claimed treatments. Examiner's Answer at page 7, line 14 through page 8, line 15; page 11, line 9 through page 12, line 3; page 25, line 18

through page 26, line 17. However, nothing in the passages cited by the Examiner says that "a patient in need of" includes all diabetics. Nor do any of the passages cited by the Examiner contradict Appellants' correct claim construction that "a patient in need of" indicates an intent to practice the claimed methods. Accordingly, the Examiner incorrectly relies on the specification to read intent out of the claims, effectively reading a limitation out of the claims.

IV. The Examiner Has Improperly Based Anticipation On More Than One Reference

The Examiner has rejected claims as anticipated by Eng, as "evidenced" by Raufman and Howard (Examiner's Answer at page 4, lines 6-9) and anticipated by Efendic as "evidenced" by Howard (Examiner's Answer at page 7, lines 3-5). The Examiner cites Howard to show that Eng "would administer" exendin-3 or exendin-4 to diabetics with the intent to improve glycemic control and improve diabetic dyslipidemia (Examiner's Answer at page 6, lines 8-10) and that Efendic "would administer" GLP-1 (7-36)amide to a diabetic patient with the intention of improving glycemic control and improving dyslipidemia (Examiner's Answer at page 9, lines 1-4).

Contrary to the Examiner's statement, Howard, does not "evidence" that the primary Eng and Efendic anticipate the claims. Under the guise of "evidence," the Examiner improperly uses Howard as motivation to modify the disclosures in Eng and Efendic to include a limitation to an intent to administer a GLP-1 agonist to treat the conditions recited in the pending claims. Although Eng and Efendic disclose only treatment of diabetes, the Examiner cites Howard to show that they "would administer" a GLP-1 agonist to diabetics with the intent to improve glycemic control and improve diabetic dyslipidemia. The Examiner's assertion that Eng or Efendic "would" administer their respective GLP-1 agonists stands in stark contrast to a clear reading of these references—i.e., that Eng and Efendic do administer a GLP-1 agonist to a diabetic patient with the

intention of improving dyslipidemia. The Examiner's use of "would" makes it clear that the he does not use Howard to "evidence" what is inherently disclosed in Eng and Efendic. Rather, the Examiner combines Howard with Eng and Efendic to read "intent" to treat conditions other than diabetes into the primary references.

Anticipation requires that all limitations of a claim be present either explicitly or inherently in a single reference. *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). It is axiomatic that anticipation does not exist if a secondary reference must be combined with a supposedly anticipatory reference to provide a limitation otherwise missing in the supposedly anticipatory reference. *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989) A secondary reference cannot be used to provide a motivation to modify a supposedly anticipatory reference to include a limitation that is not present in the supposedly anticipatory reference. Here, the Examiner has combined Eng and Efendic with Howard. The anticipation rejections based on Eng and Efendic should be reversed.

V. The Rejection of the Claims for Lack of Enablement Should Be Reversed Because the Examiner Fails to Establish a Reasonable Basis to Doubt the Objective Truth of the Teachings in the Specification

The Examiner maintains the rejection of claims 26-29 and 37-72 under 35 U.S.C. § 112, first paragraph asserting, the specification "does not reasonably provide enablement for a method of lowering one or more serum lipids, of reducing the serum LDL:HDL ratio, or of reducing the serum level of lp(A) or apo(A)." Examiner's Answer at page 14, lines 7-9. To support the enablement rejection, the Examiner relies on Juntti-Berggren, *Diabetes Care,* Vol. 19, No. 11, pp.

1200-1206 (Nov. 1996). The Examiner asserts that (Examiner's Answer at page 15, line 19 through page 16, line 3):

> [T]here is nothing in Juntti-Berggren that is inconsistent with the present specification. Therefore, Juntti-Berggren is relevant. However, Juntti-Berggren did not observe any changes in the levels of LDL and HDL cholesterol after administration of GLP-1, thereby making the full scope of the presently claimed invention suspect. Appellants have not presented any experimental data showing that a single protocol, patients' medical history, physical condition, activity, or regular diet, is correlated with the observed lack of changes in the levels of LDL and HDL cholesterol after administration of GLP-1.

Appellants first note that the Examiner applies Juntti-Berggren against all the claims. The stated basis for the rejection, however, is that Juntti-Berggren reported no changes in the levels of HDL and LDL. The Examiner does not assert that Juntti-Berggren says anything about lowering one or more serum lipids (claims 26-29, 36, and 43-55) or reducing the serum level of lp(A) or apo(A) (claims 40 and 63-72) and in fact concedes that the specification enables of lowering levels of triglycerides, free fatty acids, or cholesterol. *See* Examiner's Answer at page 14, lines 6-7.. Hence, the Examiner has no stated basis for rejecting claims directed to lowering one or more serum lipid or reducing the serum level of lp(A) or apo(A) for lack of enablement.

More generally, there is no reason to doubt the objective truth of statements in a patent application. *Fiers v. Revel*, 984 F.2d 1164, 1171-1172, 25 U.S.P.Q.2d 1601, 1607 (Fed. Cir. 1993). It is the Examiner's burden to provide a reasonable explanation of why the specification does not enable the scope of the pending claims. *In re Wright,* 999 F.2d 1557, 1561-1562, 27 U.S.P.Q.2d 510, 513 (Fed. Cir. 1993). The Examiner fails to indicate any information that is missing from the specification that would be required to make and use the claimed invention. The

Examiner has conceded, in fact, that the specification enables methods of lowering plasma levels of triglycerides, free fatty acids, or cholesterol. Examiner's Answer at page 14, lines 6-7. The specification similarly enables the claimed methods of lowering levels of one or more serum lipids, reducing the serum LDL:HDL ratio, or reducing the serum level of lipoprotein A (lp(A)) and/or apolipoprotein A (apo(A)).

First, the Examiner fails to establish that the LDL:HDL ratio of the subjects in Juntti-Berggren was outside the normal range. In the absence of a showing that the LDL:HDL ratio was outside the norm, there is no reason to expect that it would change upon administration of a GLP-1 agonist. Moreover, Juntti-Berggren is not relevant because it is a single protocol, practiced on a limited number of subjects, with no attempt to use routine optimization of dosage. Under these circumstances, the asserted failure of Juntti-Berggren to see observe changes in the levels of LDL and HDL cholesterol after administration of GLP-1 for the limited period of only 7 days and after treatment with other drugs does not make the full scope of the presently claimed methods "suspect." Drug interactions are not explained, and the length of the test may have been insufficient.

The Examiner has failed to provide a reasonable explanation of why the specification does not enable the scope of the pending claims. Appellant is under no obligation to provide any explanation of why Juntti-Berggren failed to obtain certain results. Accordingly, contrary to the Examiner's suggestion, Appellant is under no obligation to presented any experimental data showing that a single protocol, patients' medical history, physical condition, activity, or regular diet, is correlated with the results in Juntti-Berggren.

In summary, the Examiner mistakenly requires Appellants to provide evidence to prove the claims are enabled. The Examiner has failed to put forth a reasonable explanation of why

the specification does not enable one of ordinary skill in the art to make and use the full scope of the claimed invention. The enablement rejection should be reversed, accordingly.

VI. The Specification Provides Adequate Written Description for the Complete Genus of GLP-1 Agonists That Are Analogues and/or Derivatives of GLP 1(7-37), GLP-1 (7-36) amide, Exendin-3, and Exendin-4

The Examiner's asserts that the examples in the specification do not provide adequate written description for the GLP-1 agonists recited in the claims. Examiner's Answer at page 18, line 19 et seq. The Examiner's position is not consistent with current Federal Circuit law and is based on a mistaken characterization of the specification. The Federal Circuit has stated that the specification may provide adequate written description for a genus by disclosing species that are "representative of the scope" of the genus claim. *Enzo Biochem, Inc., v. Gen-Probe Incorporated,* 323 F.3d. 956, 966-967, 63 U.S.P.Q.2d 1609, 1615-16 (Fed. Cir. 2002); *The Regents of the University of California v. Eli Lilly and Company,* 119 F.3d 1559, 1569, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997). The USPTO Written Description Guidelines are also explicit that the written description requirement is satisfied for a genus when the specification implicitly or explicitly discloses "a representative number of species." *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement,* 66 Fed. Reg. 1099, 1106. As set forth in Appellants' Brief on Appeal, numerous examples of GLP-1 agonists are found in the present specification at page 12, line 15 through page 39, line 33. These examples are sufficient to demonstrate that the inventors were in possession of the genus of GLP-1 agonists.

Moreover, the Examiner asserts mistakenly that the specification fails to disclose structural features that distinguish compounds in the genus from others in the protein class. See Examiner's Answer at page 19, lines 3-13. The structures of GLP-1 (7-37), GLP-1(7-36) amide,

exendin-3, and exendin-4 were well known in the art as of the application's priority filing date. The current specification at pages 12-39 includes extensive examples of amino acid substitutions that may be made to obtain GLP-1 agonist "analogues," modifications that may be made to obtain GLP-1 agonist "derivatives," and particular species of GLP-1 agonist "derivatives," "analogues," and "derivatives of analogues." Moreover, claimed analogues and derivatives are limited to those that are similar enough in structure to the structures of GLP-1 (7-37), GLP-1(7-36) amide, exendin-3, and exendin-4 so that they retain GLP-1 agonist activity. It would be routine to identify these derivatives and analogues using assays well known in the art. *See* specification at page 40, lines 31-32.

Accordingly, the specification provides sufficient written description to show the inventors were in possession of the claimed invention when the application was filed. The rejection of the claims for lack of written description should be reversed.

VII. The Examiner Has Failed to Establish a Rationale for Indefiniteness

The Examiner asserts (Examiner's Answer at paragraph bridging pages 22-23):

> It is apparent that there is no correlation between the structure of the "analogue," "derivative," or "derivative of an analogue" recited in the present claims and the specific examples of a GLP-1 agonist or derivative disclosed in the present specification because there is no structure associated with the "analogue," "derivative," or "derivative of an analogue" recited in the present claims. Therefore, Appellants' reliance on the specific examples of such compounds to set forth the metes and bounds of an "analogue," or "derivative," "derivative of an analogue," or "exendin-4 analogue" are unpersuasive.

The Examiner is mistaken on two points. First, the present specification provides unambiguous definitions for "analogue" and "derivative" (Specification at page 41, lines 4-12):

> "An analogue" is used to designate a peptide wherein one or more amino acid residues of the parent peptide have been substituted by

> another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the parent peptide. Such addition can take place either in the peptide, at the N-terminal end or at the C-terminal end of the parent peptide, or any combination thereof.
>
> The term "derivative" is used in the present text to designate a peptide in which one or more of the amino acid residues of the parent peptide have been chemically modified, e.g., by alkylation, acylation, ester formation or amide formation.

Second, the examples set forth in the specification are all either "analogues," (i.e., they are derived from a parent GLP-1 agonist peptide by the substitution, deletion, and/or addition of one or more amino acid), "derivatives" (i.e., they are GLP-1 agonist peptides in which one or more amino acid residues of the parent peptide have been chemically modified), or "derivative of an analogue (i.e., they are derived from a parent GLP-1 agonist peptide by the substitution, deletion or addition of one or more amino acid and they further include a chemical modification of one or more residues of the peptide).

The test for indefiniteness is whether one skilled in the art would understand the metes and bounds of the claim when read in light of the specification. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986). A claim is definite if it reasonably apprises those skilled in the art of the scope of the invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The Examiner has the initial burden of demonstrating indefiniteness of the claims. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). Here, the specification provides definitions for the terms "derivative" and "analogue." The examples in the specification fall within these definitions. The Examiner has failed to put forth a reasonable explanation of why one of

ordinary skill in the art would not understand the terms "derivative," "analogue," or "derivative of an analogue," or why the specification does not advise one of ordinary skill in the art of the metes and bounds of the claims. The rejection for indefiniteness should, therefore, be reversed.

VIII. Conclusion

Based on the foregoing, in conjunction with Appellants' Appeal Brief, Appellants respectfully submit that the rejections of the claims should be reversed and the claims should be allowed.

Respectfully submitted,

Dated: June 6, 2005

Joseph R. Robinson
Registration No.: 33,448
Darby & Darby P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 753-6237 (Fax)
Attorneys/Agents For Appellant